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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/688,142	10/17/2003	William J. Curatolo	PC10805B	9233

28523 7590 08/10/2005

PFIZER INC.
PATENT DEPARTMENT, MS8260-1611
EASTERN POINT ROAD
GROTON, CT 06340

EXAMINER	
BERKO, RETFORD O	
ART UNIT	**PAPER NUMBER**
1618	

DATE MAILED: 08/10/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/688,142	CURATOLO ET AL.	
	Examiner	Art Unit	
	Retford Berko	1618	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 May 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-12,18-27,34-43,49-52,57-60,65-68 and 73-75* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-12,18-27,34-43,49-52,57-60,65-68 and 73-75* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Acknowledgement: The Amendment filed 05/09/2005 is acknowledged.

Status of Claims

Claims 13-17, 29-33, 44-48, 53-56, 61-64 and 69-72 are cancelled by applicant.

Joint Inventors

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1-12, 18-28, 34-43 and 49 remain rejected as unpatentable under 35 U.S.C. 103(a) over Myers et al (US 5, 891, 845) in view of the combination of Benet et al (US 6, 004, 927) and Curatolo et al (US 5, 605, 889).

Myers et al (Patent '845) discloses controlled release drug delivery formulations comprising cyclosporin and said composition having advantage of eliminating large blood level fluctuations when patient is taking other drugs (col 16, lin 10-19). According to Myers, verapamil; antifungals (e.g. fluconazole) and antibiotics (e.g. erythromycin) —both compounds are gp-inhibitors enhance the blood levels of cyclosporin (col 16, lin 10). Myeres further disclose the use of polymers such as polyethylene and polypropylene for achieving steady state therapeutic index in the controlled release profile (col 5, lin 30-55 and col 6, lin 1-20). Myers disclose the advantage of the formulation—reduced gastrointestinal side effects of the drug (col 6, lin 48-55).

Patent '845 does not disclose co-administration of a gp-inhibitor such as cyclosporine with azithromycin.

Benet et al (Patent '927) discloses a method for increasing bioavailability of orally administered drugs to patients wheren a drug is concurrently administered with a bioenhancer that is an inhibitor of gp-glycoprotein (abstract, and col 25, lin 20-40). Though Benet et al do not disclose the co-administration of azithromycin with a pg-inhibitor, according to Benet, ketonazole when used in combination with certain drugs increases the bioavailability of active compounds in a

drug composition e.g. enhancing the cyclosporin levels (col 21, lin 30, col 22, lin 40-60 and col 25, lin 20-40). Bennet discloses a wide range of gp-inhibitors that can be used in the formulation (quinidine, verapamil or cyclosporine—col 11, Table 1).

Curatolo et al (Patent '889) is relied upon for the disclosure dosage forms of azithromycin and a method of administering azitromycin to patients (abstract, col 6, lin 55 and col 22, lin 25-40). Curatano disclosed embodiments of controlled release azithromycin wherein having the core drug in the formulation coated with enteric polymeric materials that prevent release of the drug under acid conditions (col 15, lin 59-65), such polymers used including polyethylene oxide (col 8, lin 35-40) and co-polyalkylene oxide; including polypropylene (col 26, lin 15-25).

One of ordinary skill in the art would be motivated to administer a drug composition comprising a gp-inhibitor comprising azithromycin (a macrolide) and a gp-inhibitor (e.g. verapamil). The method of replacing azithromycin with another macrolide (ketonazole or erythromycin) on one hand is within the level of experience of one of ordinary skill in the art because as shown in the prior at cited, one of ordinary skill would expect that co-administration of the compounds (antimicrobial agent and gp-inhibitor) would reasonably lead to increase in the bioavailability of the active agent (Patent '927, col 22, lin 35-60 and col 25, lin 20-40) as well as eliminate large fluctuations of drug and thereby provide steady levels of active compound for effective therapy (Patent '845, col 16, lin 15-20). Therefore, the invention as a whole would have been prima facie obvious to one of ordinary skill at the time the invention was made.

Claims 1 and 49-60, 65-68 and 73-75 remain rejected as unpatentable under 35 U.S.C. 103(a) over Curatolo et al (US 5, 605, 889) in view of Chhabra et al (US 6, 500, 459; filed July

21, 1999) further in view of the combination of Myers et al (US 5, 891, 845) and Benet et al (US 6, 004, 927).

Curatolo et al (Patent '889) discloses azithromycin composition and a method of administering azitromycin to patients (abstract, col 6, lin 55 and col 22, lin 25-40). Patent '889 does not teach the use of the specific gp-inhibitor nelfinavir in the composition.

Chhabra et al (Patent '459) discloses polymer coated, controlled release dosage forms of verapamil-Hcl (col 21, lin 55). Patent '459 does not disclose azithromycin or any other gp-inhibitor in the composition.

As discussed, Myers et al (Patent '845) disclose controlled release drug delivery formulations comprising cyclosporin and said composition having advantage of eliminating large blood level fluctuations when patient is taking other drugs (col 16, lin 10-19). Verapamil; antifungals (e.g. fluconazole) and antibiotics (e.g. erythromycin) —both compounds are gp-inhibitors.

The disclosure in Benet et al (Patent '927) was discussed above; i.e. a method for increasing bioavailability of orally administered drugs to patients wheren a drug is concurrently administered with a bioenhancer that is an inhibitor of gp-glycoprotein (abstract, and col 25, lin 20-40). Patent '927 discloses that ketonazole when used in combination with certain drugs increases the bioavailability of active compounds in a drug composition e.g. enhancing the cyclosporin levels (col 21, lin 30, col 22, lin 40-60 and col 25, lin 20-40).

One of ordinary skill in the art would be motivated to prepare a drug composition comprising a gp-inhibitor comprising azithromycin (a macrolide) and a gp-inhibitor (e.g. verapamil). One of ordinary skill would expect that co-administration of the compounds

(antimicrobial agent and gp-inhibitor) would reasonably lead to increase in the bioavailability of the active agent (Patent '927, col 22, lin 35-60 and col 25, lin 20-40) as well as eliminate large fluctuations of drug and thereby provide steady levels of active compound for effective therapy (Patent '845, col 16, lin 15-20). The invention as a whole would have been prima facie obvious to one of ordinary skill at the time the invention was made in view of the fact that azithromycin can be replace with another macrolide (ketonazole or erythromycin and a gp inhibitor such as ketonazole or cyclosporing can be included in the composition with the reasonable expectation of obataining enhanced bioavailability of the active agents as already shown by Benet et al (Patent '927 col 25, lin 20-40).

Response To Arguments:

Applicant's arguments have been carefully considered but are found unpersuasive:

Applicant argues that the office action does not meet at least the first and third requirements foe establishing a prima facie case for obviousness i.e. (1) that there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings and (2) that there must be a reasonable expectation of success and that the prior art reference must teach or suggest all the claim limitations.

Applicants further argue that the Myers reference does not provide any specific teaching, suggestion or motivation to a skilled artisan on how to obtain the claimed method or composition comprising azithromycin and nelfinavir or a block copolymer of polytpropylene oxide) and polytethylene oxide) and that the deficiency is not cured by Benet and Curatolo and contending that one of ordinary skill in the art would not know from Myers, Benet and Curatolo how to

obtain the claimed methods and composition comprising azithromycin and nelfinavir or a block copolymer of polytpropylene oxide) and polytethylene oxide) for increasing bioavailability of azithromycin.

In response, the office action explained the motivation for one of ordinary skill in the art to prepare a drug composition comprising a gp-inhibitor comprising azithromycin (a macrolide) and a gp-inhibitor e.g. nelfinavir or verapamil-- one of ordinary skill would expect that co-administration of the compounds (antimicrobial agent and gp-inhibitor) would reasonably lead to increase in the bioavailability of the active agent (Patent '927, col 22, lin 35-60 and col 25, lin 20-40) as well as eliminate large fluctuations of drug and thereby provide steady levels of active compound for effective therapy (Patent '845, col 16, lin 15-20).

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Retford Berko** whose telephone number is 571-272-0590. The examiner can normally be reached on M-F from 8.00 am to 5.30 pm

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Thurman K Page**, can be reached on 571-272-0602.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

THURMAN K. PAGE
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600